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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,439	DOETSCH, VOLKER	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,10,14-18 and 20-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,10,14-18 and 20-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 2/13/04 is acknowledged and has been entered. Claims 11 and 89-91 have been cancelled. Claims 1, 14, and 15 have been amended. Accordingly, claims 1-4, 9, 10, 14-18, and 20-44 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

2. The rejections of claims 11 and 89-91 are now moot in light of Applicant's cancellation of the claims.

3. In light of Applicant's submission of Katz Declaration, the rejection of claims 1-4, 10, 14-17, 21, 29, 32, and 38-42 under 35 U.S.C. 102(a) as being anticipated by Serber et al. (High-Resolution Macromolecular NMR Spectroscopy Inside Living Cells, J. Am. Chem. Soc., 123: 2446-2447 (February 2001)), is hereby, withdrawn.

4. In light of Applicant's amendment, the rejection of claims 1-4, 10, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44 under 35 U.S.C. 102(b) as being anticipated by Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)), is hereby, withdrawn.

5. In light of Applicant's amendment, the rejections of claims 9, 20, 24, 25, and 35-37 under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR

Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Brown (US 817,474) and in further view of Fesik et Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) and also in view of Adams et al. (US 5,378,620), are hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 9, 10, 14-18, 20-23, and 26-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Sem (US Patent 6,333,149).

Williams et al. teach extracting structural or conformational information from NMR data set for macromolecules, i.e. overexpressed proteins (glycolytic enzymes: hexokinase (HXK, 104 kDa), phosphoglycerate kinase (PGK, 45 kDa), and pyruvate kinase (PYK)) in an intact biological compartment, i.e. intact cell (yeast Saccharomyces cerevisiae), using ^{19}F NMR (NMR detectable nucleus) longitudinal relaxation time measurements to assess their rotational mobility in the intact cells. The enzymes in the cells are labeled by biosynthetic incorporation of 5-fluorotryptophan. Williams et al. specifically determine the extent of enzyme immobilization as the result of complexation

(tight binding) to other cellular macromolecules by comparing their visibility of the ^{19}F resonances in spectra of intact cells with that of disrupted cell preparations (see Abstract, page 490, column 2, and 497, column 1). The yeast cells were prepared by transformation with one of three plasmids by operably linking (insertion) the coding sequence for the yeast enzymes into LEU-2-expressing plasmid (pKV49) where they were under the control of a PGK promoter. This non-native promoter is constructed by replacing the PGK UAS with the GAL-4 dependent GAL1-10 UAS. Expression from this vector is allowed in the presence of galactose and absence of glucose; thus, can be regulated or inhibited by manipulation of the growth medium. Restriction fragments containing the coding sequence for the enzymes were inserted into the expression site of pKV49. Some cells were transformed using URA-3-containing plasmid, pUG41S. The transformed cells were incubated (grown) in a medium, induced, labeled, then set in a buffer suspension (see page 490, column 2 to page 491, column 1: Yeast transformation and enzyme induction and Cell immobilization and perfusion). For ^{19}F NMR measurement of the conformation (rotational mobility) of the proteins in vivo, Williams et al. teach contacting the cells with radio frequency using UnityPlus 400 MHz spectrometer to excite the ^{19}F NMR, wherein the resonant frequency of ^{19}F at this field is 376.29 MHz. Williams et al. teach collecting radio frequency data; thereby producing NMR data set so as to analyze structural information of the enzymes from the data set. Viscosity of the enzymes were also measured to be 2-fold greater than viscosity of pure water (see page 491, column 2, Figures 1 and 2, and page 496, column 1). Williams et al. suggest application of these measurement studies in measuring translational

diffusion coefficients of HXK and PGK in the cell using pulse field gradient techniques, which have been used with hemoglobin in human cell, i.e. erythrocytes. Williams et al. also discuss steady increase in concentration of the protein enzymes over 24 hours after induction (see page 492, column 2). In Table 1, Williams et al. comparatively tabulates cellular enzyme activities, concentrations, and induction levels.

Williams et al. differ from the instant invention in failing to teach that the NMR data set is from multidimensional NMR method and wherein structural information is representative of a conformation of protein at a resolution sufficient to determine relative locations of two or more atoms.

Sem discloses obtaining structural information from multidimensional NMR data which is a representation of a conformation of a selected macromolecule (protein or enzyme) at a resolution sufficient to determine the relative locations of two or more atoms in a common ligand site (CL) and a specific ligand site (SL) (see column 3, line 66 to column 4, line 4, column 5, lines 8-12, column 6, lines 17-65, column 8, line 45 to column 9, line 9, and column 11, lines 28-37). The structural information may include both a first conformation of the enzyme (first stage) and a second conformation of the enzyme (second stage) (see column 10, lines 22-64). The enzyme may have a molecular weight of 5 kDa, 25 kDa or 70 kDa (see column 4, lines 4-12). The enzyme can be obtained from human, mammals, plants (eukaryotic), yeast (fungi) or bacteria which may be in tissue cultures or suspension (see column 4, lines 19-26). The enzyme can be labeled with deuterium (see column 7, lines 2-8). Sem teaches determining which atoms are proximal to the SL site when a mimic is bound to the CL

site. These atoms are identified by first determining which amino acids of the macromolecule are proximal to the SL site and then identifying which atoms on the bound CL mimic are proximal to the amino acids (column 1, lines 48-60 and column 2, lines 3-21). In practice, Sem teaches using multidimensional NMR methods such as triple resonance NMR including HMQC, HSQC, TROSY, and HNCA (see columns 9 and 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teaching of Sem in multidimensional NMR methods for obtaining structural information representative of macromolecular conformations at a resolution sufficient to determine relative locations of two or more atoms, into the NMR method applied to intact biological cells as taught by Williams because Sem specifically taught that multidimensional NMR methods are capable of resolution sufficient to determine relative atoms of interest and their locations in enzyme ligands to thus, provide rapid, effective generation and accurate screening of combinatorial libraries of ligand drug candidates.

Williams et al. and Sem have been discussed supra. Williams et al. and Sem differ from the instant invention in failing to teach concentration levels of the macromolecules, i.e. proteins, in the biological compartments, i.e. cells; in claim 27, 0.3% compared to the total weight of the cell and in claim 28, up to 50% compared to the total weight of the cell.

It is, however, maintained that induction of protein expression so as to reach specific levels of concentration in comparison to the total weight of the cell within which

it resides, are all result effective variables which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 27 and 28 are for any particular purpose or solve any stated problem and both Williams and Sem teach that in NMR spectroscopic art, protein expression induced to specific levels in comparison to the total weight of the cell, often vary according to the sample being analyzed or label being used, and various other parameters appear to work equally as well; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art by normal optimization procedures.

7. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Sem (US Patent

6,333,149) as applied to claims 1-4, 9, 10, 14-18, 20-23, and 26-44 above, and further in view of Adams et al. (US 5,378,620).

Williams et al. and Sem have been discussed supra. Williams et al. and Sem differ from the instant invention in failing to disclose administering a sufficient amount of inhibitor such as rifampicin, to the cell to cause inhibition of transcription in the cell.

Adams et al. disclose rifampicin as an antibiotic that inhibits RNA polymerase in bacteria, i.e. E. coli, that exhibits LEU-2-expressing plasmid. NMR Spectroscopy, using ^{15}N, ^{1}H, ^{13}C, ^{13}P and ^{2}H is used in studying bacterial protein structure in solution as effected by rifampicin inhibition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer an inhibitor such as rifampicin such as taught by Adams, to a bacterial cell for example, to inhibit transcription in the cell, or to a yeast cell transformation by operably linking the coding sequence for the yeast enzymes into LEU-2-expressing plasmid as taught by Williams as modified by Sem because rifampicin as taught by Adams provides selective inhibition effects to transcription in cells that are under the control of specific promoters, while otherwise allowing study of structural information in desired protein structures, i.e. overexpressed proteins, using NMR Spectroscopy.

Response to Arguments

8. Applicant's arguments with respect to claims 1-4, 9, 10, 14-18, and 20-44 have been considered but are moot in view of the new grounds of rejection.

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
May 13, 2004

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641